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STOMACH

# Mortality study of 18 000 patients treated with omeprazole

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**Background:** The long term safety of potent gastric acid suppressive therapy has yet to be established.
**Method:** General practice record review at a median interval of 26 months followed by retrieval of details of all deaths within four years using the UK National Health Service Central Registers in 17 936 patients prescribed omeprazole in 1993–1995. Death rates were compared with general population rates.
**Results:** Records of 17 489 patients (97.5%) were examined. A total of 12 703 patients received further scripts for antisecretory drugs, 8097 for omeprazole only (65.6%): 3097 patients have died. All cause mortality was higher in the first year (observed/expected (O/E) 1.44 (95% confidence intervals (CI) 1.34–1.55); p<0.0001) but had fallen to population expectation by the fourth year. There were significant mortality increases in the first year, falling to or below population expectation by the fourth year, for deaths ascribed to neoplasms (1.82 (95% CI 1.58–2.08); p<0.0001), circulatory diseases (1.27 (95% CI 1.13–1.43); p<0.0001), and respiratory diseases (1.37 (95% CI 1.12–1.64); p<0.001). Increased mortality ascribed to digestive diseases (2.56 (95% CI 1.87–3.43); p<0.0001) persisted, although reduced. Increased mortality rates for cancers of the stomach (4.06 (95% CI 2.60–6.04); p<0.0001), colon and rectum (1.40 (95% CI 0.84–2.18); p=0.075), and trachea, bronchus, and lung (1.64 (95% CI 1.19–2.19); p<0.01) seen in the first year had disappeared by the fourth year but that for cancer of the oesophagus had not (O/E 7.35 (95% CI 5.20–10.09) (p<0.0001) in year 1; 2.88 (95% CI 1.62–4.79) (p<0.001) in year 4). Forty of 78 patients dying of oesophageal cancer had the disease present at registration. Twenty seven of those remaining cases had clinical evidence of Barrett's disease, stricture, ulcer, or oesophagitis at registration (O/E 3.30 (95% CI 2.17–4.80)). Six deaths occurred in patients with hiatal hernia or reflux only (O/E 1.02 (95% CI 0.37–2.22)) and five in patients without oesophageal disease (O/E 0.77 (95% CI 0.25–1.80)). No relationships were detected with numbers of omeprazole scripts received.
**Conclusions:** Increases in mortality associated with treatment are due to pre- existing illness, including pre-existing severe oesophageal disease. There was no evidence of an increased risk of oesophageal adenocarcinoma in those without oesophageal mucosal damage recorded at registration.

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The introduction of any new class of drugs, such as the proton pump inhibitors (PPIs), where usage is likely to be widespread and prolonged, requires that safety during chronic treatment is assured. The need for such assessment is emphasised by claims that omeprazole treatment might adversely affect the management of upper gastrointestinal cancer because amelioration of symptoms and re-epithelialisation of the cancer might be promoted, so hindering disease recognition.[1] It has also been suggested that raised serum gastrin concentrations in response to reduced acidity might act as growth promoters,[2] or that treatment might accelerate the onset of atrophic gastritis, so predisposing to gastric cancer.[3] Moreover, as omeprazole is commonly used to treat gastro-oesophageal reflux disease, it is important to determine whether treatment influences the frequency of oesophageal adenocarcinoma, a tumour known to complicate oesophageal metaplasia (Barrett's disease), which occurs in association with oesophageal reflux associated damage.

We examined mortality rates from any cause over a four year period during or after treatment with omeprazole in six cities in England and Scotland. Death rates were compared with those expected nationally. Data have strength in relating risks to those observed in the general population, as done previously by us for cimetidine.[4–6]

## METHOD

We sought to register a cohort of 18 000 patients prescribed omeprazole in the six UK conurbations of or surrounding Birmingham, Glasgow, Newcastle, Nottingham, Oxford, and Portsmouth. Using the computerised registers of cooperating general practitioners, we identified takers of omeprazole in the period 1993–1995. Records of patients who were still alive and who had received at least one prescription for omeprazole were examined and details taken of, inter alia, the patient's age, sex, and NHS number, prescription data, and the reasons for any prescription, together with details of any prior diagnosis of malignant disease, any previous upper abdominal surgical procedures, and any other recorded antisecretory drug use in the previous 12 months. We excluded from consideration all those dying prior to the registration date.

Clinical diagnoses were those recorded in individual case notes and were not re- interpreted, but details of investigations were recorded. Individual diagnoses of ulcer, oesophagitis, Barrett's oesophagus, hiatal hernia or reflux, and cancer required specific mention of these following investigation.

**Abbreviations:** O/E, observed/expected; PPI, proton pump inhibitor; NHSCR, National Health Service Central Register; ICD, International Classification of Disease.

**Table 1** Major diagnostic groups of patients prescribed omeprazole

| | % Men (8409) | % Women (9527) | % with 6 or more scripts in year before recruitment* |
|---|---|---|---|
| Oesophageal ulcer | 2.8 | 2.1 | 39.6 |
| Other oesophageal disease | 48.7 | 49.8 | 30.3 |
| Gastric ulcer | 3.3 | 3.3 | 25.9 |
| Other gastric disease | 7.6 | 6.5 | 24.0 |
| Duodenal ulcer | 10.9 | 5.7 | 22.3 |
| Other duodenal disease | 6.7 | 3.5 | 23.7 |
| Gastrointestinal symptoms not otherwise specified | 32.8 | 37.4 | 18.9 |
| Prophylaxis | 1.0 | 1.5 | 27.6 |
| Unclear | 3.2 | 3.3 | 20.1 |

Diagnostic figures add up to more than 100% because some patients had more than one diagnosis.
*A single script is equivalent to one month of treatment at a standard dosage.

Records of patients registered were re-examined after two years, and new diagnoses of oesophageal cancer at hospital attendance and details of subsequent omeprazole and other antisecretory drug prescribing were recorded. Patients transferring to another general practitioner were followed by post or visit to the practice if nearby. The records of cohort members were also flagged at the National Health Service Central Register (NHSCR) in England and Scotland, providing data on all causes of death and confirmation of cancer diagnoses.

Observed death rates, classified according to the ninth revision of the International Classification of Disease (ICD), were compared with expected population rates in England and Scotland using published data from the Office of National Statistics. For this purpose, rates were based on those individuals dying in 1996, the approximate midpoint of the study period, taking account of age, within five year groups, and sex. In addition, death rates were examined in relation to the number of scripts received by patients for omeprazole, as noted at the time of registration. Relative risks presented are the ratios of observed to expected deaths, together with their 95% confidence intervals (CI) throughout, alongside the observed and expected numbers of deaths.

The study was approved by local ethics committees and by the Office of National Statistics. It was also constructed to conform to the guidelines for safety assessment of marketed medicines (SAMM guidelines),[7] and was registered with the Medicines Control Agency of the UK.

## RESULTS

A total of 17 936 patients had been registered by December 1995 when entry was completed, and clinical follow up data were available after two years in 17 489 (97.5%) patients. Mean age of the patients at registration was 59.6 years (median 61.5; range 7–105) with 46.9% being men. In the year prior to registration, 38% had received 1–2 omeprazole prescriptions while 25% had received six or more. Table 1 shows the major diagnostic groupings in patients prescribed omeprazole. Oesophageal disease and gastrointestinal symptoms of uncertain cause formed the bulk of the indications. There were 12 501 diagnoses of oesophageal disease recorded. Oesophagitis (3664), reflux not otherwise specified (3842), and hiatal hernia (3142) were the commonest recorded but with substantial numbers of patients with stricture (791), ulcer (441), or Barrett's disease (417) of the oesophagus. Oesophageal disease was pre-existing cancer in 40 and was not clearly specified in the remaining 164.

We found that 2096 patients (11.7%) had undergone a total of 2477 upper abdominal procedures in the past. Commoner procedures were cholecystectomy (1014 (5.3%)), oesophageal surgery (489 (2.7%)) and elective ulcer surgery (439 (2.4%)). Further prescriptions for antisecretory treatments had been received by 12 703 (72.6%) of 17 489 patients with two year follow up data; 10 929 (62.5%) had received at least one further prescription for omeprazole with 8097 having omeprazole alone.

Table 2 shows that observed mortality tended to be higher in the first year after registration and then fell overall to population

**Table 2** Observed (O) deaths from all causes and observed deaths divided by deaths expected* (O/E) in each study year

| | | | | | Study year | | | |
|---|---|---|---|---|---|---|---|---|
| Site | n | Mean age (y) | % Men | | 1 | 2 | 3 | 4 |
| All patients | | | | | | | | |
| Birmingham | 3001 | 58.3 | 46.8% | O | 120 | 74 | 86 | 60 |
| | | | | O/E | 1.6 | 1.0 | 1.1 | 0.8 |
| Glasgow | 3128 | 58.3 | 43.7% | O | 117 | 89 | 81 | 79 |
| | | | | O/E | 1.3 | 1.0 | 0.9 | 0.9 |
| Newcastle | 3514 | 58.5 | 48.9% | O | 143 | 126 | 115 | 74 |
| | | | | O/E | 1.7 | 1.5 | 1.4 | 0.9 |
| Nottingham | 3012 | 60.6 | 48.0% | O | 131 | 110 | 107 | 95 |
| | | | | O/E | 1.5 | 1.3 | 1.2 | 1.1 |
| Oxford | 2318 | 60.6 | 45.2% | O | 76 | 75 | 76 | 57 |
| | | | | O/E | 1.1 | 1.1 | 1.1 | 0.8 |
| Portsmouth | 2963 | 61.6 | 48.1% | O | 137 | 117 | 101 | 108 |
| | | | | O/E | 1.4 | 1.2 | 1.1 | 1.2 |
| Total | 17 936 | 59.6 | 46.9% | O | 724 | 591 | 566 | 473 |
| | | | | O/E | 1.4 | 1.2 | 1.2 | 1.0 |

*Expected deaths based on national (England and Wales) rates for 1996, except for Glasgow which is based on Scottish rates for 1996, and total rates which are based on pooled Scotland, England, and Wales expected deaths. Calculations made for each sex separately within five year age groupings.

**Table 3** Observed and expected number of deaths for individual ICD (International Classification of Disease) chapters

| | | Study year | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | Exp/year |
| 001–139 | Infectious/parasitic diseases | 8 (3.1)* | 4 (1.5) | 2 (0.8) | 2 (0.8) | 3 |
| 140–239 | Neoplasms | 217 (1.8)* | 160 (1.3)* | 147 (1.2)* | 116 (1.0) | 119 |
| 240–279 | Endocrine, nutritional | 7 (1.1) | 7 (1.1) | 5 (0.8) | 10 (1.6) | 6 |
| 280–289 | Blood disorders | 1 (0.6) | 1 (0.6) | 1 (0.6) | 3 (1.7) | 2 |
| 290–319 | Mental disorders | 5 (0.5) | 8 (0.9) | 6 (0.6) | 5 (0.5) | 9 |
| 320–389 | Nervous system | 4 (0.5) | 5 (0.7) | 7 (0.9) | 5 (0.7) | 8 |
| 390–459 | Circulatory system | 284 (1.3)* | 237 (1.1) | 251 (1.1)* | 190 (0.9)* | 224 |
| 460–519 | Respiratory system | 112 (1.4)* | 93 (1.1) | 87 (1.1) | 80 (1.0) | 82 |
| 520–579 | Digestive system | 45 (2.6)* | 35 (2.0)* | 35 (2.0)* | 28 (1.6)* | 18 |
| 580–629 | Genitourinary system | 11 (1.7) | 11 (1.7) | 7 (1.1) | 8 (1.2) | 7 |
| 680–709 | Skin/subcutaneous tissue | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 |
| 710–739 | Musculoskeletal system | 8 (2.6)* | 5 (1.6) | 6 (1.9) | 10 (3.2)* | 3 |
| 740–759 | Congenital anomalies | 0 (0.0) | 1 (2.3) | 2 (4.7) | 0 (0.0) | 0 |
| 780–799 | Symptoms/ill defined | 10 (1.1) | 13 (1.5) | 5 (0.6) | 11 (1.2) | 9 |
| 800–999 | Injury and poisoning | 10 (1.1) | 11 (1.2) | 6 (0.6) | 11 (1.2) | 9 |
| Total | | 722 | 591 | 567 | 479 | 500 |

Observed/expected (O/E) ratios in parentheses.
*O/E significantly >1.0, p<0.05.

expectation, with similar trends in the six conurbations. Table 3 shows the mortality observed for individual ICD chapters by year, together with their associated relative risks (observed/expected (O/E)). Mortality was initially higher than expected for neoplasms (observed 217, expected 119; O/E 1.82; 95% CI 1.58–2.08; p<0.0001) and also for diseases of the circulatory (observed 284, expected 224; O/E 1.27; 95% CI 1.13–1.43; p<0.0001), respiratory (observed 112, expected 82; O/E 1.37; 95% CI 1.12–1.64; p<0.001), and digestive (observed 45, expected 18; O/E 2.56; 95% CI 1.87–3.43; p<0.0001) systems. Death rates from neoplasms fell to population expectation by year 4, as did those for the circulatory and respiratory systems. Greater mortality than expected was also initially recorded for infectious and parasitic disease (O/E 3.09; 95% CI 1.33–6.08; p<0.01), falling to population expectation by the fourth year of the study. Initially increased mortality from musculoskeletal disorders, upper gastrointestinal disorders, and chronic liver disease, although falling with time towards population expectation, still tended to remain raised.

Table 4 shows the observed and expected deaths for selected ICD rubrics, including major gut epithelial cancers and cancer of the lung, breast, and blood forming tissues, ischaemic and cerebrovascular disease, and upper gastrointestinal causes. For all selected causes, initial increases in mortality declined towards or below population expectation, except for oesophageal cancer and liver disease which remained significantly above expectation.

To examine results for oesophageal cancer in more detail, we stratified data in those without oesophageal cancer at registration according to whether patients were recorded initially as having Barrett's disease, oesophageal ulcer, stricture, or oesophagitis (categorised as severe disease), or whether they had reflux or hiatal hernia without Barrett's disease, ulcer, stricture, or oesophagitis (categorised as mild disease). Table 5 shows the types of non- malignant oesophageal disease present in the 38 patients diagnosed as having oesophageal cancer after registration. Among those with severe oesophageal disease, 27 died of oesophageal cancer (expectation 8.2 in four years; O/E 3.30; 95% CI 2.17–4.80). In contrast, of those with mild oesophageal disease, evidenced by clinical diagnoses of reflux or hiatal hernia, only six died of oesophageal cancer (expectation 5.9; O/E 1.02; 95% CI 0.37–2.22). In those without initial clinical diagnoses of oesophageal disease, five patients died (against expectation 6.5; O/E 0.77; 95% CI 0.25–1.80). Of the 417 who had Barrett's disease identified at some time and recorded at registration, nine had died of oesophageal cancer (O/E 11.25; 95% CI 5.14–21.36).

In those with severe oesophageal disease, the risk of developing oesophageal cancer was slightly lower (observed 8, expected 2.8; O/E 2.86; 95% CI 1.23–5.63) in those who had received six or more scripts in the year before registration than in those who had received fewer (observed 19, expected 5.2; O/E 3.65; 95% CI 2.20–5.71). Examination of mortality from all other neoplasms, and from all other (non-neoplastic)

**Table 4** Observed and expected number of deaths for selected ICD (International Classification of Disease) rubrics

| | | Study year | | | | |
|---|---|---|---|---|---|---|
| All patients | | 1 | 2 | 3 | 4 | Exp/year |
| 150.0–150.9 | Malignant neoplasm, oesophagus | 36 (6.9)* | 17 (3.3)* | 8 (1.6) | 15 (2.9)* | 5.2 |
| 151.0–151.9 | Malignant neoplasm, stomach | 25 (6.1)* | 15 (2.5)* | 7 (1.2) | 4 (0.9) | 5.9 |
| 153.0–154.1 | Malignant neoplasm, colon and rectum | 19 (1.4) | 20 (1.5) | 19 (1.4) | 12 (0.9) | 13.6 |
| 162.0–162.9 | Malignant neoplasm, trachea and lung | 45 (1.6) | 33 (1.2) | 36 (1.3) | 28 (1.0) | 27.6 |
| 174.0–174.9 | Malignant neoplasm, female breast | 11 (1.1) | 15 (1.5) | 11 (1.1) | 9 (0.9) | 9.8 |
| 200.0–208.0 | Lymphoma, myeloma, leukaemia | 15 (1.9)* | 12 (1.5) | 16 (2.1)* | 6 (0.8) | 7.8 |
| 410.0–414.9 | Ischaemic heart disease | 169 (1.4)* | 142 (1.2)* | 143 (1.2)* | 108 (0.9) | 119.3 |
| 430–438 | Cerebrovascular disease | 64 (1.1) | 56 (1.0) | 59 (1.0) | 41 (0.7) | 58.8 |
| 530–537.9 | Disease of oesophagus, stomach, and duodenum, and GI haemorrhage | 10 (2.2)* | 13 (2.9)* | 10 (2.2)* | 5 (1.1) | 4.5 |
| 571–571.9 | Chronic liver disease and cirrhosis | 16 (6.0)* | 11 (4.1)* | 7 (2.6)* | 7 (2.6)* | 2.7 |
| Total | | 410 | 334 | 316 | 235 | 255.1 |

Observed/expected (O/E) ratios in parentheses.
*O/E significantly >1.0, p<0.05.

**Table 5** Observed and expected deaths from cancer of the oesophagus in successive years according to initial oesophageal disease diagnosis in those cancer free at registration

| Initial oesophageal diagnosis | Expected No/year | Observed by year | | | | | O/E (95% CI) |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | Total | |
| Barrett's disease/ulcer/stricture/oesophagitis (n=5517) | 2.0 | 7 | 5 | 6 | 9 | 27 | 3.30 (2.17–4.80) |
| (Barrett's disease cases only)* (n=417) | (0.2) | (2) | (1) | (3) | (3) | (9) | 11.25 (5.14–21.36) |
| Hiatal hernia or reflux only (n=6984) | 1.5 | 1 | 1 | 1 | 3 | 6 | 1.02 (0.37–2.22) |
| No oesophageal diagnosis (n=5435) | 1.6 | 3 | 1 | 1 | 0 | 5 | 0.77 (0.25–1.80) |
| Total | 5.2 | 11 | 7 | 8 | 12 | 38 | 1.85 (1.31–2.54) |

O/E, observed/expected.
*Includes all diagnoses of the condition, irrespective of date of diagnosis.

causes, likewise showed no relationship with the intensity of treatment. Clear histological diagnoses were available in 29 of 38 oesophageal cancer cases diagnosed after the study enrolment date. Fifteen (83%) of 18 patients with adenocarcinomata had initial clinical diagnoses of oesophagitis, oesophageal ulcer, stricture, and/or Barrett's oesophagus. In contrast, only five (45%) of 11 patients with squamous cancers had such initial diagnoses (p=0.086, Fisher's exact test).

## DISCUSSION

By registering patients with the NHSCR, we systematically collected information on the causes of death over four years in nearly 18 000 patients prescribed omeprazole. Mortality was significantly greater than population expectation in the first year after registration, falling progressively to that expectation by the fourth year. Increased mortality in the first year is unlikely to reflect drug effects because it was detectable for a wide variety of causes and was unrelated to the duration of initial treatment. Furthermore, very similar patterns were observed in our previous studies of cimetidine takers conducted in the same way.[5 6] We deduce therefore that confounding by indication for treatment explains the general patterns observed. Thus treatment of chest pain attributed to reflux, but actually anginal in origin, could well explain increased cardiovascular disease mortality. Use of omeprazole in those perceived to be at high risk of ulcer complications is also likely to explain raised risks of death from peptic ulcer disease and musculoskeletal disease.[8] This finding should not be taken to imply that such treatment fails in its objectives: there is strong evidence from controlled trials to indicate that treatment is appropriate and successful.[9–11] In the same way, increased mortality from musculoskeletal diseases seems likely to reflect use of omeprazole in those perceived as at risk of ulcer complications.[12] The increased mortality observed from infectious and parasitic disease in the first two years of observation lacks a plausible explanation but may represent the play of chance in small numbers. PPI use is known to be associated with an increased frequency of dysenteric infections but not with death from this cause.[13 14] Persistently increased mortality from chronic liver disease in our cohort seems likely to represent deaths in patients with upper gastrointestinal symptoms coincident liver disease, and common epidemiological features in smoking and drinking.[15 16] Scrutiny of our cases revealed none where a causal relationship with antisecretory treatment seemed likely. Prescribing of omeprazole to attendees at general practitioner surgeries with other main complaints, a form of Berkson's bias,[17] would be expected to lead to increases in mortality from a broad range of complaints, particularly in the early period after prescription, a phenomenon seen in our previous studies of cimetidine.

Examination of the data for neoplastic diseases showed that mortality increases were particularly high for gastric and oesophageal cancer in the first year after registration. This almost certainly represents confounding by indication rather than an adverse drug effect, or masking of disease by treatment. The patterns are similar to those seen with cimetidine; no dose relationship was seen with treatment, and death rates fell progressively with time. Persisting increases into the fourth year were only seen for oesophageal cancer. The majority of those dying with oesophageal cancer had initial diagnoses suggesting severe oesophageal disease, namely Barrett's disease, stricture, ulcer, or oesophagitis. Observed mortality was more than three times as great as expected in these patients whereas it was not increased in those with initial diagnoses of hiatal hernia or reflux, or in those initially considered to have disease outside the oesophagus as the reason for omeprazole prescription. Patients with adenocarcinomata were six times as likely to have initial clinical diagnoses suggesting severe underlying oesophageal disease as those with squamous tumours. Observed mortality was more than 10 times as high in patients in whom Barrett's disease had been detected at some time in their clinical course whether or not found at registration. However, findings of high proportions of Barrett's disease in this group may reflect the results of differences in intensity of surveillance in those with and without malignant disease.

Although in the long term follow up of approximately 10 000 patients prescribed cimetidine we found no evidence that treatment was likely to cause gastric or other varieties of gastrointestinal cancer,[4–6] it has recently been suggested that histamine receptor antagonist treatment might predispose to cardio-oesophageal adenocarcinoma .[18] That claim was based on comparing prior drug intake in cardio-oesophageal cancer patients with that in individuals with myocardial infarction. The nature of the control would seem to make sensible deductions about causation impossible. Our findings indicate strongly that the nature of the underlying oesophageal disease is the major, and probably sole, cause of the raised risk of oesophageal cancer death in our omeprazole takers. This conclusion is reinforced by evidence that death rates were unrelated to the number of omeprazole scripts received at registration. This finding is consonant with findings that the proportions of patients receiving acid suppressant therapy for Barrett's oesophagus, and oesophagitis without Barrett's disease, did not differ significantly.[19] The data in our study suggest strongly that underlying oesophageal disease explains the increased risk of oesophageal cancer but it should be noted that classification depended upon reports available to us in practice case records, these not being produced to standardised criteria. The actual strength of risk is therefore uncertain. Systematic study has suggested that there may be publication bias in the reporting of cancer risks in Barrett's oesophagus.[20] Our data show, compared with the findings of others, rather moderate increases in the risk of oesophageal cancer. Our set has particular strengths. Firstly, patients for study were selected prior to the outcomes being known. Secondly, the

population studied was large, and the follow up prolonged and complete. Thirdly, the number of incident oesophageal tumours diagnosed after enrolment (38) was large.

It has been suggested that, based on symptoms alone, patients with oesophageal reflux are at nearly eight fold increased risk of adenocarcinoma.[21] Our data indicate that in our population, any increase in oesophageal cancer risk may be confined to those with evidence of mucosal structural damage, and that simple symptomatic reflux may not pose significant risks. This conclusion is consonant with that of Cohen and Parkman[22] that structural damage, and Barrett's oesophagus in particular, are the critical factors. Our data showing a fall in gastric cancer death rates by the fourth year of the study to slightly below population expectation suggest that gastric cancer risk is neither intrinsically raised in the population studied nor influenced in the period under review by omeprazole or other antisecretory drug prescribing. Our results are reassuring given concern that treatment might cause early gastric atrophy,[23 24] although any increased incidence of gastric atrophy associated with antisecretory treatment might take longer than the period under review to influence mortality from gastric cancer. We conclude that treatment with omeprazole per se did not increase the risks of dying from general or neoplastic disease. Our data also suggest that raised risks of oesophageal malignancy are associated with underlying severe oesophageal disease.

## APPENDIX

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